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# Liver sinusoidal endothelial cells in hepatic fibrosis: opportunities for future strategies

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ABSTRACT

Liver sinusoidal endothelial cells (LSECs) are highly specialized endothelial cells that form the interface between the hepatic vasculature and parenchymal cells, playing a crucial role in maintaining hepatic homeostasis. Under pathological conditions, LSECs undergo capillarization, marked by the loss of fenestrae and formation of a basement membrane, thereby impairing microcirculation and promoting fibrosis. Beyond capillarization, LSECs experience a spectrum of pathological changes—including angiogenesis, endothelial-to-mesenchymal transition (EndMT), autophagy, and senescence—all of which contribute to fibrogenesis through distinct molecular pathways. Moreover, LSECs orchestrate liver fibrotic remodeling through dynamic crosstalk with hepatic stellate cells (HSCs), hepatocytes, Kupffer cells, and immune cells, exerting both pro- and anti-fibrotic effects. This review comprehensively summarizes LSECs dysfunction in hepatic fibrosis, with a particular focus on intercellular communication and emerging therapeutic strategies. Elucidating the regulatory networks that govern LSECs behavior may uncover new opportunities for the diagnosis and treatment of chronic liver disease.

## 1. Introduction

The liver is primarily composed of parenchymal and non-parenchymal cells. Parenchymal cells account for approximately 80 % of the total liver volume, whereas LSECs, the most abundant non-parenchymal liver cells, account for approximately 3 % of the total liver volume and 15 %–20 % of all hepatocytes. LSECs are specialized endothelial cells lining the hepatic sinusoids and function as critical regulators of nutrient exchange, immune tolerance, and vascular homeostasis within the liver microenvironment [1].

Recent single-cell and spatial omics analyses have unveiled notable functional and transcriptional heterogeneity among LSECs along the portal-central axis. Specifically, periportal LSECs exhibit high expression of immune regulatory markers such as CD34 and von Willebrand factor (VWF), whereas pericentral LSECs preferentially express pro-angiogenic factors (e.g., Wnt2, Rspo3) and regeneration-associated markers (e.g., Oit3) [2,3]. This zonation-dependent specialization determines how LSECs respond differently to physiological and pathological cues, thereby influencing disease progression and regenerative responses.

Under pathological conditions, LSECs undergo profound phenotypic alterations, including loss of fenestrations and the formation of a continuous basement membrane—a process termed capillarization [4]. DeLeve et al. first demonstrated that LSECs capillarization precedes the onset of hepatic fibrosis, suggesting that LSECs act as a gatekeeper in the initiation of fibrogenesis [5]. Subsequent studies across various fibrosis models, such as carbon tetrachloride ($CCl_4$)-induced and diet-induced (e.g., CDAA, MCD) liver injury, have consistently supported this temporal sequence. In these models, early loss of LSECs fenestrae and reduced endothelial nitric oxide synthase (eNOS) activity precede HSCs activation and extracellular matrix (ECM) accumulation [6–8]. Similarly, in non-alcoholic steatohepatitis (NASH), LSECs dysfunction has been identified as an early event that precedes overt fibrotic remodeling [9]. However, it is important to acknowledge that this sequence may not be universally applicable. In chronic or advanced liver injury models, LSECs capillarization and HSCs activation may occur concurrently or engage in a pathological feedback loop. Thus, while LSECs capillarization is frequently an initiating event in fibrogenesis, its primacy may be context-dependent.

Beyond capillarization, LSECs undergo other significant pathological changes during fibrosis progression, including aberrant angiogenesis, endothelial-to-mesenchymal transition (EndMT), dysregulated

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autophagy, and cellular senescence. These complex alterations are mediated by distinct molecular pathways and profoundly influence hepatic inflammation, fibrosis, and regeneration dynamics. Furthermore, accumulating evidence indicates that paracrine interactions between LSECs and other hepatic cells—including HSCs, hepatocytes, Kupffer cells, and infiltrating immune cells—are essential for orchestrating the hepatic microenvironment during fibrosis progression.

In this review, we comprehensively summarize recent advances regarding LSECs dysfunction in hepatic fibrosis, emphasizing the underlying molecular mechanisms and cellular crosstalk. We also highlight potential therapeutic strategies targeting LSECs dysfunction, which may offer novel interventions for chronic liver diseases.

## 2. LSECs undergo various pathological changes

### 2.1. Capillarization

Capillarization, also known as dedifferentiation, is a key phenotypic alteration in LSECs characterized by the loss of fenestrations, deposition of a laminin- and collagen IV-rich basement membrane, platelet endothelial cell adhesion molecular (PECAM) expression at intercellular junctions, and dysregulation of key markers such as VEGFR2, eNOS, *p*-eNOS, and LYVE-1 [10,11]. This process disrupts bidirectional molecular exchange between hepatocytes and hepatic sinusoids, reducing sinusoidal compliance and increasing vascular resistance, thereby impairing liver function [12]. Notably, capillarization is an early event in fibrosis pathogenesis, as LSECs in both pre-fibrotic and fibrotic livers lose their ability to maintain HSCs quiescence, thereby contributing to disease progression [6] (Fig. 1).

The molecular mechanisms underlying LSECs capillarization have been extensively investigated, revealing both pro-fibrotic and protective pathways. Adipocyte fatty acid-binding protein (A-FABP) promotes capillarization via Hedgehog signaling [13], while endothelial IVA phospholipase A2 (IVA-PLA2), a key enzyme in the arachidonic acid cascade, enhances sinusoidal capillarization, ultimately driving HSCs activation and fibrosis [7]. Additionally, vascular cell adhesion molecule 1 (VCAM1) on LSECs contributes to this process through Hippo/Yap1 signaling [14], whereas JAM-A deficiency exacerbates this process via Hedgehog and VEGFR1/2 signaling, further enhancing HSCs activation [15]. Hypoxia-driven mechanisms have also been implicated, with the HIF-1α/CXCR4/PDGF-BB/CXCR7 axis contributing to LSECs capillarization and promoting a fibrogenic microenvironment [16]. Recently, deep learning models show that hypoxia induces chromatin remodeling through HIF-1α, promoting periportal LSECs to transition to a pro-fibrotic phenotype, while pericentral LSECs maintain regenerative potential through the Wnt/β-catenin pathway [17]. Given the central role of LSECs capillarization in fibrosis pathogenesis, targeting its key molecular drivers represents a promising therapeutic strategy.

### 2.2. Angiogenesis

Hepatic sinusoidal angiogenesis, driven by dysfunctional LSECs and abnormal angioarchitecture, is another hallmark of hepatic fibrogenesis [18]. Notably, this angiogenic response exhibits biphasic dynamics

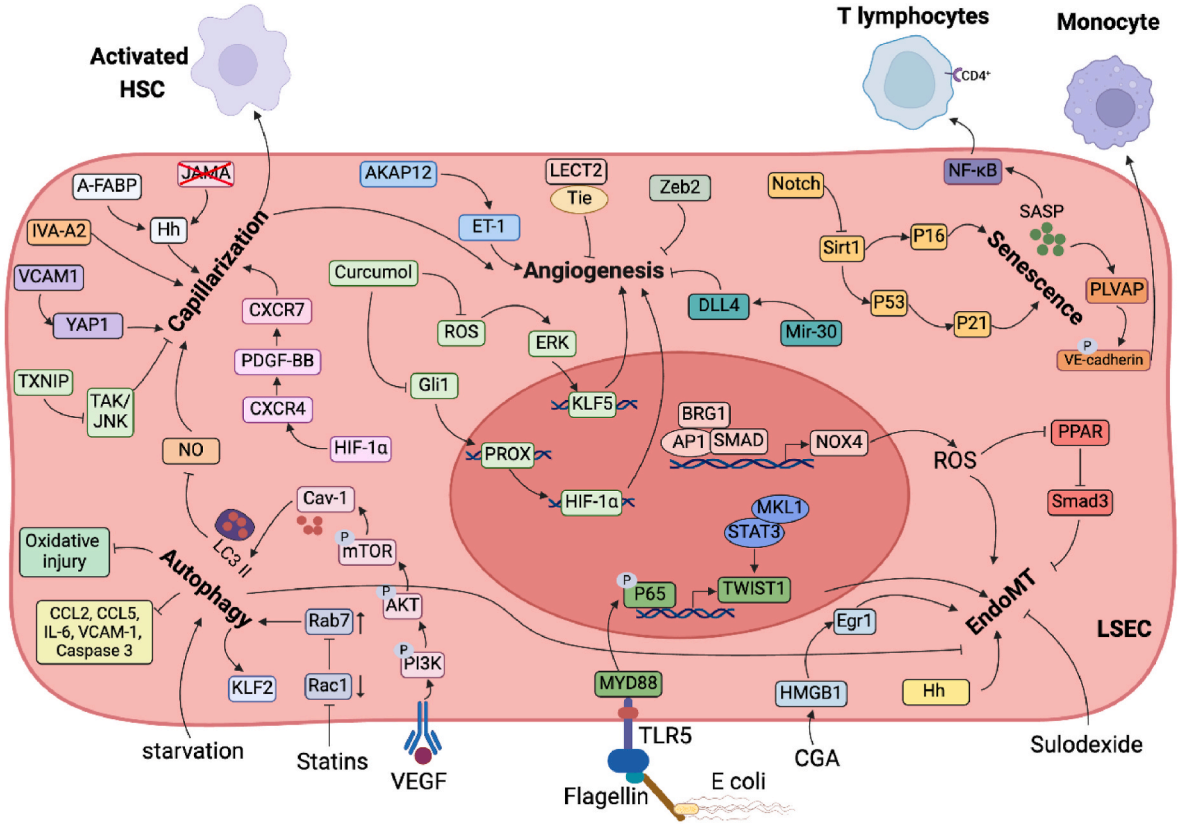


**Fig. 1.** Pathological Changes in Differentiated LSECs during Liver Fibrosis. During liver fibrosis, differentiated LSECs undergo pathological changes, including capillarization, angiogenesis, autophagy dysregulation, endothelial-to-mesenchymal transition (EndMT), and senescence, all of which contribute to fibrosis progression and impaired liver function. Capillarization disrupts molecular exchange between hepatocytes and sinusoids, promoting HSCs activation and ECM deposition, with key regulators including JAM-A, A-FABP, IVA-A2, VCAM1, TXNIP, NO, and HIF-1α. LSECs-driven angiogenesis, which varies across fibrosis stages, affects nutrient exchange and hepatocyte injury, modulated by AKAP12, Curcumol, Zeb2, miR-30, and LECT2. Autophagy plays a dual role in fibrosis, either protective or detrimental depending on context, with pathways such as VEGF-PI3K–AKT–MTOR and Statins-Rac1-Rab7-KLF2 involved. EndMT leads to ECM deposition and fibrosis, regulated by the Hedgehog pathway, TGF-β, Twist1, Erg1, and NOX4. Senescent LSECs exhibit oxidative stress and pro-inflammatory signaling, deteriorating the hepatic microenvironment, with Notch, NF-κB, and PLVAP as key regulators.

throughout disease progression, transitioning from a compensatory mechanism in early fibrosis to a pathogenic driver in later stages [19].

In the early stage of fibrosis, angiogenesis is markedly elevated as a compensatory response to hypoxia and tissue remodeling. HIF-1α accumulation under hypoxic conditions induces VEGF and other pro-angiogenic factors, promoting neovascularization to restore oxygen supply—but at the cost of disturbing hepatocyte–sinusoid exchange and aggravating parenchymal stress. Curcumol, through inhibition of the Glis–PROX1–HIF-1α axis, has been shown to restrain LSECs-driven angiogenesis, suggesting that targeted modulation of this axis may preserve microvascular balance in early injury [20]. Similarly, A-kinase anchoring protein 12 (AKAP12), a negative regulator of endothelial remodeling, attenuates angiogenesis by inhibiting basement membrane formation and endothelin-1 (ET-1) expression, thereby dampening fibrogenic signaling [21]. LECT2, acting via Tie1 dephosphorylation, inhibits endothelial migration and sprouting angiogenesis in the portal region, contributing to vascular stability [22].

In advanced fibrosis, angiogenesis declines due to accumulation of insoluble ECM and microvascular rarefaction, yet it paradoxically contributes to sinusoidal capillarization and vascular distortion, both of which exacerbate hypoxia and fibrosis progression [20]. LECT2, while inhibiting portal angiogenesis, paradoxically promotes sinusoidal capillarization, suggesting a dual, context-dependent effect that worsens microvascular fibrosis [23]. Endothelial zinc finger E-box-binding homeobox 2 (Zeb2) preserves hepatic angioarchitecture and exerts a protective role against fibrosis [23]. Mechanistically, ECM stiffening (≥12 kPa) in late-stage fibrosis activates YAP/TAZ–PKP2 signaling, inducing CXCR4 and PDGF-BB expression in LSECs, which fosters vascular remodeling and HSCs recruitment [19] (Table 1).

Altogether, these findings underscore the stage-specific roles of LSECs-mediated angiogenesis: regenerative in early injury, yet maladaptive in chronic fibrosis. Therapeutic strategies must therefore account for the temporal and spatial dynamics of vascular remodeling to achieve optimal antifibrotic outcomes.

**Table 1**
LSECs pathological changes with mechanisms.

| LSECs Pathological Change | Key Molecules | Major Pathways | Ref. |
|---|---|---|---|
| Capillarization | A-FABP, IVA-PLA2, VCAM1, JAM-A, HIF-1α, TXNIP, Fibronectin (FN), Collagen fibrils | A-FABP -Hedgehog, VCAM1-YAP, JAM-A -VEGFR1/2, HIF-1α/CXCR4/PDGF-BB, HIF-1α-Wnt/β-catenin, TXNIP-TAK1/JNK, FN/TLR4–NOTCH–HES1–STAT3, Collagen fibrils/DDR2–JAK2/PI3K/AKT–Myocardin | [7,13–16,19,59,93,94] |
| Angiogenesis | VEGF, HIF-1α, LECT2, AKAP12, Zeb2, MiR-30c, Curcumol | Glis–PROX1–HIF-1α, LECT2/Tie1/MAPK, AKAP12-Endothelin-1, miR-30c/DLL4/Notch, Curcumol-ROS/ERK-KLF5/LDH-A | [20–23,128–131] |
| Autophagy | eNOS, Atg7, Rac1, Rab7, SIRT1, CCL2, CCL5, IL-6, VCAM-1, α-SMA, TGF-β1, Collagen-1α2, cleaved caspase-3, Cav-1 | eNOS/sGC/cGMP, Rac1/Rab7–KLF2, Sirt1–P53–P21 or Sirt1–P16,Cav-1-F-actin-NO | [25–29,132–134] |
| EndMT | TGF-β, MKL1, BRG1, HMGB1, TWIST1, *Escherichia coli, Mechanical stretch-induced* | TGF-β–Twist1, MKL1/STAT3/Twist1, BRG1/SMAD3/AP-1–NOX4, HMGB1-Egr1, *Escherichia coli*/TLR5–MyD88–TWIST1, Mechanical stretch- Smad3-PPARγ | [31–40] |
| Senescence | p16, PLVAP, ET-1, TNF-α, IL-1, IL-6, SASP | PLVAP/VE-cadherin/NF-κB, Notch/DLL4–ET-1, NF-κB | [43–48] |

### 2.3. Autophagy

Autophagy is a cell survival mechanism that monitors the balance between synthesis and degradation of cellular components [24]. While extensively characterized in hepatocytes and cholangiocytes, increasing evidence supports a critical role for autophagy in regulating LSECs phenotype, fenestration, and pro-fibrotic potential. Multiple studies demonstrate that autophagy plays a dual, stage-specific role in LSECs during liver disease progression. In early-stage fibrosis, autophagy is largely protective. For example, $H_2O_2$-induced oxidative stress activates both nucleophagy and cytoplasmic autophagy, which help preserve LSECs fenestration and prevent cytoskeletal collapse [25,26]. Transmission electron microscopy (TEM) has confirmed the presence of autophagosomes in nutrient-deprived LSECs, indicating active autophagy under physiological stress [27]. Additionally, statins promote LSECs autophagic activity via Rac1 inhibition and Rab7 activation, leading to upregulation of KLF2 and improved microvascular function [28]. Supporting this, Atg7 deletion in LSECs exacerbates $CCl_4$-induced fibrosis, elevating oxidative stress and hepatic stellate cell (HSCs) activation without significantly altering hepatic inflammation [8].

In contrast, during advanced fibrosis, dysregulated or impaired autophagy contributes to LSECs dysfunction and fibrogenesis. For example, autophagy impairment observed in LSECs from NASH patients is associated with elevated expression of inflammatory cytokines (e.g., CCL2, CCL5, IL-6, VCAM-1), EndMT markers (e.g., α-SMA, TGF-β1, Collagen-1α2), and apoptotic proteins (e.g., cleaved caspase-3), all of which exacerbate fibrosis [29].

Collectively, these findings highlight a biphasic regulation of autophagy in LSECs: protective in the early stages by mitigating oxidative injury and maintaining sinusoidal structure, yet detrimental in chronic liver injury by contributing to endothelial dysfunction, senescence, and fibrogenesis. These insights underscore the potential of stage-specific autophagy modulation as a therapeutic approach in liver fibrosis.

### 2.4. EndMT

EndMT is a dynamic process in which endothelial cells lose their characteristic markers and cell–cell junctions while acquiring mesenchymal properties, contributing to hepatic fibrosis [27]. In LSECs, EndMT has been proposed as one mechanism underlying the loss of fenestrae and gain of ECM-producing capacity during liver injury. Recent studies using advanced models such as liver-on-a-chip (LOAC) have provided direct in vitro evidence of LSECs-EndMT during fibrosis progression [30]. Moreover, activation of Hedgehog signaling and exposure to lipopolysaccharide (LPS) can induce mesenchymal-like phenotypes in cultured LSECs [31]. However, the existence of EndMT in LSECs in vivo remains controversial. Su et al. reported that although primary rat LSECs undergo EndMT in vitro, they did not observe this process in fibrotic or cirrhotic mouse livers, as evidenced by single-cell transcriptomic profiling [32]. These discrepancies may stem from several factors. First, EndMT in LSECs is often partial or incomplete, characterized by increased ECM synthesis and loss of fenestrae, but without a complete transition to motile mesenchymal cells [38]. Such intermediate states may be difficult to detect using conventional markers. Second, species- and model-specific differences may influence LSECs plasticity. For example, rat and mouse LSECs respond differently to TGF-β and inflammatory cues, and the fibrosis etiology (e.g., $CCl_4$, MCD, NASH) may variably activate EndMT-related pathways. Third, the hepatic microenvironment, including hypoxia, inflammatory cytokines, mechanical forces, and gut microbiota-derived factors (e.g., LPS, flagellin), may significantly influence LSECs plasticity and modulate EndMT

susceptibility. These contextual differences across models may underlie inconsistent observations regarding LSECs-EndMT in vivo. Further lineage tracing and single-cell studies are needed to resolve these discrepancies.

Mechanistically, EndMT in LSECs appears to be driven by multiple signaling pathways. Capillarized LSECs exhibit partial EndMT, characterized by ECM overproduction without enhanced cell mobility, leading to perisinusoidal ECM deposition and worsening fibrosis [33]. The transcriptional regulators MKL1 and STAT3 cooperatively promote TGF-β-induced EndMT via Twist1 activation, exacerbating fibrosis [34]. Similarly, BRG1, through interactions with SMAD3 and AP-1, induces NOX4 expression, facilitating ROS-dependent EndMT [35]. In addition, HMGB1 has been shown to enhance EndMT through Egr1, while chlorogenic acid (CGA) attenuates this effect and reduces ECM production [36,37].

Recent studies have also identified microbial and mechanical factors influencing EndMT. *Escherichia coli* triggers EndMT via the TLR5/MYD88/TWIST1 pathway, linking gut microbiota to NAFLD progression [38]. Additionally, mechanical stretch-induced Smad3 phosphorylation, exacerbated by PPARγ downregulation, promotes EndMT in endothelial cells [39]. Therapeutically, sulodexide has been shown to counteract LSECs capillarization and EndMT, providing hepatoprotective effects [40].

Altogether, while LSECs-EndMT is supported by in vitro mechanistic studies, its pathological significance and existence in vivo remain under debate. Future investigations using endothelial lineage tracing and single-cell resolution in different species and disease models are essential to clarify the relevance of EndMT in hepatic fibrosis.

### 2.5. Senescence

Cellular senescence, first described by Hayflick and Moorhead [41], is a form of irreversible cell cycle arrest that prevents undesired proliferation [42]. In LSECs, senescence is characterized by sustained cell cycle arrest, macromolecular damage, a senescence-associated secretory phenotype (SASP), and metabolic dysregulation [43]. Upon injury, LSECs transition into SASP, leading to basement membrane disruption, fenestrae loss, and increased expression of senescence markers and inflammatory mediators, including nitric oxide (NO), TNFα, IL-1, and IL-6 [44,45]. These changes create a pro-inflammatory microenvironment that enhances leukocyte adhesion and exacerbates hepatic inflammation. Senescent LSECs contribute to liver pathology by disrupting sinusoidal homeostasis and intercellular communication. Laurent et al. identified senescent endothelial cells in the liver and found that their selective elimination ($p16^{High}$ cells) paradoxically induced hepatic fibrosis [46]. Additionally, SASP-driven NF-κB activation has been shown to regulate immune cell recruitment, further amplifying inflammation [47]. aspUpregulation of plasmalemma-vesicle-associated protein (PLVAP) in senescent LSECs enhances monocyte transmigration by modulating endothelial permeability through phospho-VE-cadherin regulation [48]. These findings suggest that targeting senescent LSECs is a promising strategy for improving liver repair and regeneration.

Given the detrimental effects of LSECs senescence on hepatic homeostasis and regeneration, targeting senescence pathways presents a promising therapeutic strategy. More broadly, interventions that modulate capillarization, angiogenesis, autophagy, EndMT, or senescence in LSECs may provide new avenues for mitigating chronic liver disease progression and promoting tissue repair.

## 3. Sinusoidal crosstalk in hepatic fibrosis

The hepatic lobule consists of hepatocytes and non-parenchymal cells (NPC) associated with hepatic sinusoids, including LSECs, Kupffer cells (KCs), pit cells, dendritic cells, and HSCs [49]. The primary mechanisms involved in the development of hepatic fibrosis include LSECs capillarization, HSCs activation, HCs apoptosis, and KCs activation [50,51]. LSECs capillarization potentially serving as a preliminary step necessary for fibrogenesis [9,52,53]. Therefore, systematically analyzing the role of LSECs in autocrine and paracrine signaling in the fibrotic microenvironment may help identify targets for early detection and treatment of hepatic fibrosis.

### 3.1. LSECs and HSCs

#### 3.1.1. Crosstalk between differentiated LSECs and Quiescent HSCs

In the healthy liver, HSCs serve as retinoid (vitamin A) storage cells and are distributed in the space of Disse between LSECs and HCs [54,55]. Under pathological conditions, HSCs transition into an activated state, characterized by proliferation, contractility, depletion of retinoid stores, and excessive extracellular matrix (ECM) deposition, including collagen types I and III, α-SMA, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) [56]. HSCs activation is a pivotal event in fibrosis progression. Differentiated LSECs play a critical role in maintaining HSCs quiescence and preventing fibrosis. Through direct signaling and paracrine interactions, LSECs regulate the hepatic microenvironment to suppress HSCs activation. Understanding the molecular mechanisms underlying LSECs-HSCs crosstalk is essential for elucidating hepatic fibrosis pathogenesis and developing targeted antifibrotic therapies (Fig. 2).

*3.1.1.1. Nitric oxide (NO).* NO, a vasodilation agent, is produced by LSECs and hepatic endothelial cells through endothelial nitric oxide synthase (eNOS), playing a crucial role in maintaining sinusoidal homeostasis and regulating HSCs activity [57]. NO production is modulated by several signaling pathways. Erk1/2 promotes a pro-regenerative LSECs phenotype by increasing the NO-to-ROS ratio, thereby inhibiting HSCs activation and supporting tissue repair, while Akt fosters a profibrotic LSECs phenotype by reducing NO availability, leading to HSCs activation and senescence [58]. Liu et al. demonstrated that Src-Akt signaling regulates eNOS activation via the G-protein-coupled receptor kinase-interacting protein 1 (GIT1) scaffold, facilitating NO production. Additionally, thioredoxin-interacting protein (TXNIP) deletion in LSECs induces sinusoidal capillarization and inflammation by suppressing NO synthesis, an effect mediated through the TAK1/JNK pathway [59]. Hwang et al. further showed that endothelial TAZ enhances NO production by activating Nos3 transcription via KLF2, thereby inhibiting LSECs capillarization and reducing fibrosis [60]. Moreover, the lncRNA Airn sustains LSECs differentiation and HSCs quiescence through the KLF2–eNOS–sGC axis [61].

LSECs-derived NO regulates HSCs through three primary mechanisms: (1) Inhibition of Activation: NO prevents HSCs activation, as evidenced by studies where NO synthase inhibition disrupts LSECs-mediated HSCs quiescence [10]. Additionally, NO modulates prostaglandin E2 signaling, further suppressing HSCs proliferation and chemotaxis [62]. (2) Inhibition of Migration: NO suppresses HSCs migration via cGMP-dependent PKG signaling, which inhibits Rac1 pathway activation [63,64]. (3) Induction of Apoptosis: NO promotes apoptosis in activated HSCs through a mitochondrion- and ROS-dependent, caspase-independent mechanism [65].

*3.1.1.2. Vascular endothelial growth factor (VEGF).* VEGF, primarily secreted by HSCs and hepatocytes, plays a crucial role in maintaining LSECs phenotype and function. DeLeve et al. demonstrated that VEGF is essential for preserving LSECs differentiation, as co-culture with hepatocytes or LSECs restored VEGF-dependent endothelial characteristics lost upon VEGF inhibition [66]. Similarly, Junji et al. found that VEGF-mediated maintenance of LSECs fenestrations is NO-dependent [67]. while May et al. reported that liver-specific VEGF depletion led to fenestration loss and HSCs activation, promoting fibrosis [68]. These findings support VEGF's anti-fibrotic role in early injury through NO–sGC–cGMP signaling and fenestration preservation. However, in

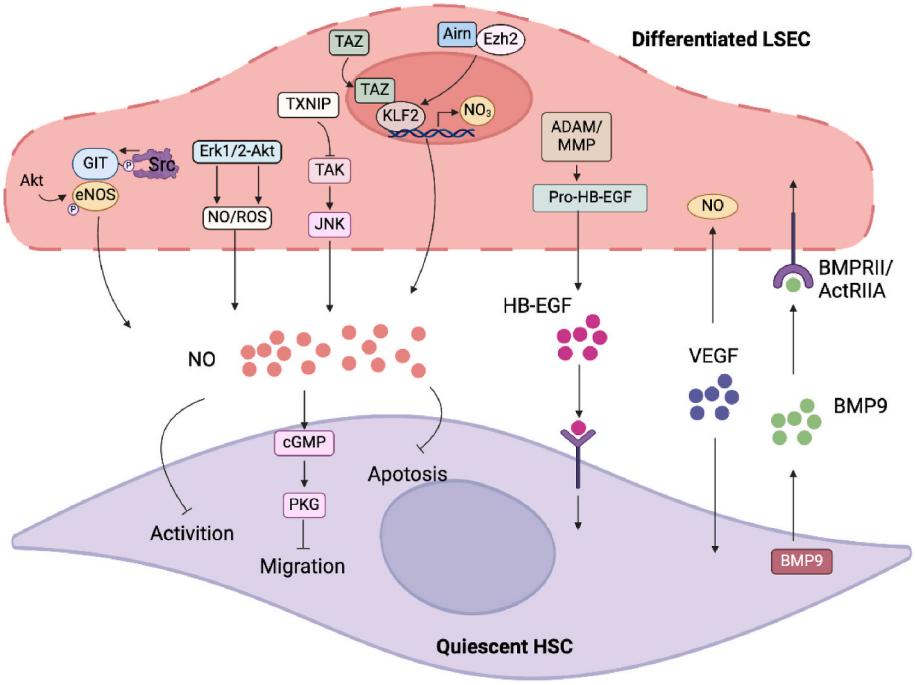


**Fig. 2.** Crosstalk between Differentiated LSECs and Quiescent HSCs. NO signaling is essential for sinusoidal function and HSCs quiescence. Src and Akt facilitate eNOS activation via the GIT1 scaffold, while Erk1/2 sustains the pro-regenerative phenotype of LSECs by enhancing the NO/ROS ratio, inhibiting HSCs activation, and promoting tissue repair. TXNIP suppresses the TAK1/JNK pathway, restoring NO production, while TAZ and lnc-Airn regulate Nos3 transcription and KLF2-eNOS-sGC signaling, respectively, maintaining LSECs differentiation and HSCs quiescence. Additionally, HB-EGF, processed by ADAM/MMP-mediated cleavage, and VEGF support LSECs fenestration and HSCs quiescence. BMP9 acts in a paracrine manner to preserve LSECs differentiation and fenestrae, reinforcing the endothelial barrier and preventing fibrosis.

advanced fibrosis, VEGF exhibits paradoxical pro-fibrotic effects. Despite increased VEGF ligand levels in cirrhotic livers [69], downstream signaling is impaired due to reduced expression of its key receptors, Kdr (VEGFR2) and Nrp1, particularly in zone 3 LSECs, as revealed by single-cell RNA sequencing [32]. This receptor downregulation, coupled with ECM stiffening and hypoxia, redirects VEGF activity from vascular homeostasis toward pathological angiogenesis, mediated via VEGFR2/PDGFR-β crosstalk, DLL4/Notch signaling, and YAP/TAZ activation. These processes promote neutrophil recruitment, collagen IV deposition, and further sinusoidal remodeling [70]. Moreover, LSECs zonation along the porto-central axis contributes to this dichotomy. Zone 3 LSECs, which exhibit the highest levels of capillarization and metabolic stress, are more susceptible to fibrogenic reprogramming. They upregulate glycolytic enzymes and pro-inflammatory chemokines [71], while periportal zone 1 LSECs maintain higher levels of VEGFR2 and anti-inflammatory genes [32]. These spatial differences underscore the importance of zonation-specific therapeutic strategies.

Altogether, VEGF serves as a context- and zone-dependent regulator of LSECs–HSCs crosstalk. Its protective or pathogenic role hinges on injury stage, receptor availability, and microenvironmental cues. Therapeutic targeting of VEGF must therefore be precisely timed and spatially informed to prevent fibrosis progression while preserving sinusoidal function.

*3.1.1.3. Heparin-binding EGF-like growth factor (HB-EGF).* Capillarization in hepatic fibrosis is driven, in part, by the incomplete differentiation of bone marrow (BM)-derived LSECs recruited to injured liver tissue [6]. DeLeve et al. demonstrated that HB-EGF plays a crucial role in maintaining HSCs quiescence. This process is mediated by the cleavage and release of the HB-EGF ectodomain via the ADAM/MMP family, facilitating LSECs-HSCs interactions. In cirrhotic livers, immature LSECs lose this regulatory function due to the downregulation of sheddases necessary for HB-EGF processing, leading to sustained HSCs activation and fibrosis progression [6].

*3.1.1.4. Bone morphogenetic protein 9 (BMP9).* HSCs-derived BMP9 is a key regulator of LSECs differentiation and sinusoidal integrity. Agnès et al. demonstrated that BMP9 binds to its high-affinity receptor ALK1 or low-affinity receptor ALK2, along with the co-receptor endoglin, forming heterocomplexes with BMPR2 or ActRIIA on LSECs [72]. This paracrine signaling preserves LSECs fenestrations and protects against perivascular fibrosis.

LSECs-HSCs interactions are bidirectional, with differentiated LSECs maintaining HSCs quiescence through NO, HB-EGF, and VEGF signaling, while HSCs-derived BMP9 and VEGF sustain LSECs fenestrations. Understanding the LSECs secretome and its regulatory network may uncover novel therapeutic targets for hepatic fibrosis.

*3.1.2. Communication between capillarized LSECs and activated HSCs*

Capillarization disrupts the bidirectional exchange of molecules between hepatocytes and hepatic sinusoids, restricting toxins to specific regions, leading to sustained liver damage, enhancing the activation of HSCs, and eventually promoting fibrogenesis (Fig. 3).

*3.1.2.1. Endothelin-1 (ET-1).* ET-1, initially identified in endothelial cell supernatants by Yanagisawa [73], plays a pivotal role in LSECs dysfunction and fibrosis progression. ET-1 promotes LSECs defenestration [74] while failing to activate NO synthase, contributing to endothelial dysfunction [75,76]. Chen et al. demonstrated that LSECs from $CCl_4$-treated mice exhibit reduced eNOS and *p*-eNOS levels but increased ET-1 expression, correlating with fibrosis severity. Mechanistically, DLL4 signaling enhances HSCs coverage of sinusoids by upregulating ET-1 production in LSECs [77]. Additionally, TGR5 activation via cAMP suppresses ET-1 transcription in LSECs, thereby reducing ET-1-induced HSCs contraction through ETRA binding [78]. In cirrhosis, elevated ET-1 levels, along with upregulated ETAR and ETBR, contribute to

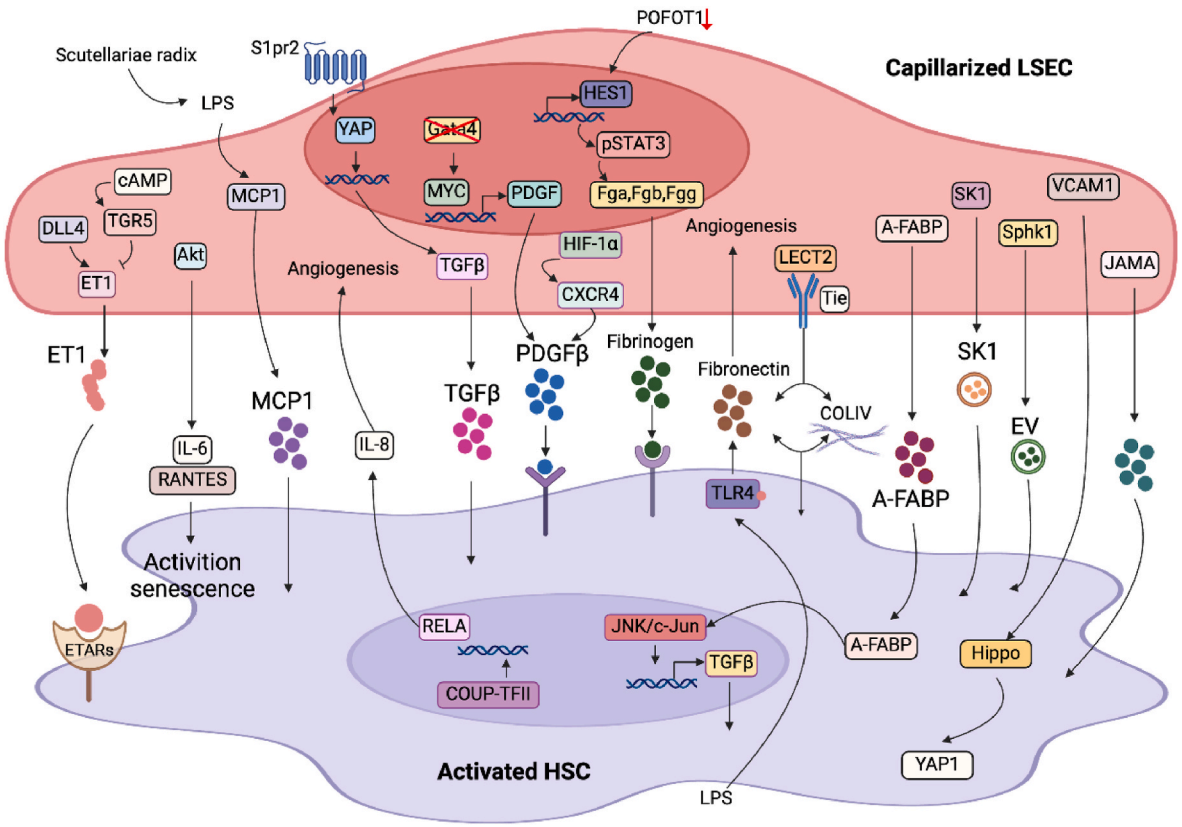


**Fig. 3.** Crosstalk between capillarized LSECs and activated HSCs. Capillarized LSECs and activated HSCs engage in reciprocal signaling that drives fibrosis progression. DLL4 enhances sinusoidal HSCs coverage by upregulating ET-1 in LSECs, while TGR5 activation via cAMP suppresses ET-1 transcription, preventing HSCs contraction through ETAR. LSECs secrete inflammatory factors (IL-8, IL-10, RANTES, MCP-1) to promote HSCs activation. TGF-β production is stimulated by S1PR2, and PDGF-BB is upregulated via Gata4, both acting in a paracrine manner to sustain HSCs activation. Loss of POFUT1 increases fibrinogen expression through NOTCH/HES1/STAT3 signaling. LPS-induced fibronectin production via TLR4 promotes LSECs angiogenesis, while LECT2-Tie1 interaction enhances ECM deposition by releasing collagen IV and fibronectin. LSECs-derived A-FABP facilitates TGFβ1 transactivation in HSCs via JNK/c-Jun signaling, reinforcing fibrogenic activation. Exosome Sphk1 and SK1 from LSECs further stimulate HSCs activation. Additionally, LSECs-derived VCAM1 activates HSCs via the Hippo/YAP1 pathway, and endothelial JAM-A promotes HSCs activation through paracrine signaling.

increased hepatic sinusoidal microvascular tone, exacerbating portal hypertension and fibrosis progression.

*3.1.2.2. Inflammatory factors.* Chronic liver injury triggers the secretion of immunogenic and inflammatory cytokines from LSECs, including TNFα, MIP-1α, MIP-1β, MIP-2, MCP-1, RANTES, IL-10, and IL-17, which contribute to fibrosis progression [58,79]. Profibrotic LSECs secrete IL-10 and RANTES, activating HSCs via Akt signaling and inducing their senescence [58]. Additionally, capillarized LSECs modulate hepatic immune tolerance, further promoting fibrosis [79]. Inflammatory crosstalk between LSECs and HSCs is bidirectional. HSCs can drive LSECs capillarization through paracrine signaling. For instance, COUP-TFII expression in HSCs enhances LSECs migration and angiogenesis via the NF-κB/RELA/IL-8 pathway [80]. Notably, Scutellariae radix has been shown to attenuate LPS-induced LSECs activation, reduce MCP-1 expression, and suppress HSCs migration in a rat model, suggesting its potential antifibrotic effects [81].

*3.1.2.3. TGF-β and PDGF.* Capillarized LSECs contribute to hepatic fibrosis by secreting profibrotic cytokines, including TGF-β and PDGF, which directly activate HSCs [82,83]. Recently, Liao et al. demonstrated that sphingosine-1-phosphate receptor 2 (S1pr2) signaling in LSECs promotes nuclear translocation of YAP, upregulating TGF-β expression and inducing HSCs activation in a paracrine manner [84]. Winkler et al. reported that Gata4 deficiency in LSECs leads to MYC-mediated upregulation of PDGFB, exacerbating fibrosis in a CDAA diet-induced liver injury model. This GATA4/PDGFB axis was further validated in cirrhotic human endothelial cells [85]. Additionally, HIF-1α-induced LSECs capillarization enhances CXCR4 expression and PDGF-BB secretion. PDGF-BB binds to PDGFR-β on LSECs, promoting capillarization, while its interaction with PDGFR-β on HSCs drives their activation and fibrogenesis [16].

*3.1.2.4. Extracellular vesicles (EVs).* EVs are nanoscale membrane-bound particles that mediate intercellular communication and have been increasingly recognized as critical regulators of liver fibrosis. Recent studies have shown that EVs are involved in the communication between healthy LSECs and HSCs. Vijay et al. demonstrated that EC-derived exosomes containing sphingosine kinase 1 (SK1) promote HSCs migration and activation via fibronectin-integrin interactions and dynamin-dependent internalization, contributing to fibrosis progression [86,87]. Transcriptomic analysis by Manicardi et al. revealed that LSECs-derived EVs from chronic liver disease models are enriched in angiocrine effectors and tropomyosin 1, with the latter exhibiting anti-fibrotic properties by inactivating HSCs [88]. Supporting this, Wang et al. reported that LSECs-derived EVs suppress HSCs proliferation and inflammatory gene expression, further indicating their regulatory role in fibrosis [89]. These findings underscore the complexity of EV-mediated LSECs-HSCs communication and highlight exosomes as potential therapeutic targets for modulating hepatic fibrosis (Table 2).

*3.1.2.5. ECM.* Hepatic fibrosis is primarily characterized by ECM deposition, with contributions from multiple cell types beyond HSCs [90,91]. While activated HSCs are the predominant source of type I

**Table 2**
EV-mediated intercellular communication in liver fibrosis.

| EV Source | Target Cell | Fibrotic Effect | Key Cargo | Mechanism/ Outcome | Ref. |
|---|---|---|---|---|---|
| LSECs | HSCs | Pro-fibrotic | SK1 | Promotes HSCs migration and activation via fibronectin-integrin-S1P signaling | [86, 87] |
| LSECs | HSCs | Anti-fibrotic | Tropomyosin 1, | Inhibits HSCs activation and ECM production | [88] |
| LSECs | KCs | Anti-inflammatory | Not specified | Suppresses KCs inflammatory gene expression | [89] |
| HCs | LSECs | Pro-fibrotic | ITGβ1 | Enhances monocyte adhesion to LSECs; promotes inflammation and capillarization | [105, 106] |

collagen, LSECs, following capillarization, primarily synthesize type IV collagen and laminin, further altering the hepatic microenvironment and perpetuating fibrosis [92]. Excessive ECM deposition alters the local microenvironment and further promotes HSCs activation, accelerating the development of hepatic fibrosis. Zhu et al. demonstrated that FN mediates TLR4-dependent interactions between HSCs and LSECs, with LPS-induced FN production in HSCs promoting LSECs angiogenesis, which in turn enhances HSCs activation [93,94]. Endothelial POFUT1 suppresses FN expression, mitigating its profibrotic signaling via the NOTCH/HES1/STAT3 axis, suggesting a potential antifibrotic target [94]. Mechanotransduction also influences fibrosis progression. Liu et al. established fibrotic microniches (FμNs) in which condensed collagen fibrils act as mechanical transducers, activating HSCs through the DDR2–JAK2/PI3K/AKT–myocardin pathway [19]. Additionally, immune cells contribute to LSECs capillarization via LECT2-Tie1 interactions, upregulating MAPK-dependent PPAR signaling and driving ECM protein release, including collagen IV and FN [22]. These findings highlight the complex interplay between ECM dynamics, LSECs, and HSCs in fibrosis progression, underscoring potential therapeutic targets for intervention.

*3.1.2.6. Adipocyte fatty acid binding protein (A-FABP).* A-FABP, also known as aP2 and FABP4, is an adipokine that primarily acts as a chaperone to transport fatty acids between cellular organelles or into the circulation to regulate lipid metabolism [95]. In chronic liver injury, LSECs upregulate and secrete A-FABP, which promotes capillarization via Hedgehog (Hh) signaling, thereby facilitating HSCs activation. Additionally, LSECs-derived A-FABP diffuses into HSCs, where it induces JNK/c-Jun-mediated transactivation of TGFβ1, further amplifying HSCs activation and ECM deposition in a paracrine manner. This cascade enhances fibrogenic cytokine expression and scar matrix accumulation, contributing to hepatic fibrosis progression [13]. Targeting A-FABP signaling may represent a novel therapeutic strategy for mitigating fibrosis.

*3.1.2.7. Adhesion molecules.* Adhesion molecules play a critical role in hepatic fibrosis by mediating LSECs-HSCs interactions. Junctional adhesion molecule A (JAM-A), highly expressed in human viral fibrosis, regulates leukocyte extravasation. Brozat et al. demonstrated that endothelial JAM-A deficiency enhances HSCs activation, suggesting a paracrine role of LSECs in fibrogenesis, though further validation is needed [15]. Additionally, Guo et al. reported that LSECs-derived VCAM1 activates the Yes-associated protein 1 (YAP1) pathway, promoting HSCs activation and accelerating fibrosis progression [14].

### 3.2. Communication between LSECs and HCs

Hepatocytes (HCs), the most abundant liver cell type, play a critical role in maintaining liver function [96]. Liver injury disrupts HCs-LSECs interactions, contributing to inflammation, apoptosis, HSCs activation, and excessive ECM deposition—key drivers of hepatic fibrosis. Capillarization leads to sinusoidal structural distortion and fenestrae loss, reducing permeability and impairing the exchange of oxygen, nutrients, and metabolic factors. This disruption induces hepatocyte ischemic atrophy, fibrosis, and compensatory hypertrophy [97]. Impaired HCs-LSECs crosstalk further hinders liver regeneration, promoting maladaptive healing and fibrosis progression toward cirrhosis [11,98]. Understanding the molecular mechanisms underlying HCs-LSECs interactions is crucial for developing targeted antifibrotic therapies (Fig. 4).

LSECs secrete hepatocyte growth factor (HGF) and Wnt2, key cytokines that regulate liver regeneration [99]. Following partial hepatectomy, VEGFR2 signaling in LSECs suppresses ID1 expression, promoting Wnt2 and HGF release to stimulate hepatocyte proliferation [99]. Wnt2 functions as an LSECs-specific autocrine growth factor, synergizing with VEGFR2 to enhance regenerative signaling [100]. After acute liver injury, CXCR7 and CXCR4 upregulation in LSECs induces ID1 expression, further stimulating HGF and Wnt2 secretion to drive regeneration. Erk1/2 signaling reinforces this pro-regenerative phenotype by upregulating HGF and Wnt2 expression [58]. Additionally, Substance P counteracts TNF-α-induced endothelial dysfunction and enhances HGF secretion from LSECs, supporting hepatocyte regeneration in a paracrine manner [101]. Endothelial transcriptional regulation also influences regenerative capacity. Gata4 deficiency impairs hepatic metabolic zonation by downregulating Wnt2 and Bmp2, hindering regeneration [85]. Similarly, the lncRNA Airn enhances hepatocyte proliferation by promoting Wnt2a and HGF secretion from LSECs [61].

LSECs-derived factors play a critical role in regulating liver regeneration and fibrosis. During the inductive phase of liver regeneration, Ang2 expression in LSECs is transiently downregulated, suppressing TGFβ1-mediated hepatocyte inhibition and thereby facilitating hepatocyte proliferation [82]. As regeneration progresses into the angiogenic phase, Ang2 expression is restored, controlling LSECs proliferation via VEGFR2 signaling in an autocrine manner. This LSECs-hepatocyte crosstalk serves as a key regulatory mechanism in liver regeneration [82]. In fibrosis, CD147 is highly expressed in both hepatocytes and LSECs in $CCl_4$-induced liver injury. Yan et al. demonstrated that CD147 upregulates VEGF-A secretion in hepatocytes via the PI3K/Akt pathway while enhancing VEGFR2 expression in LSECs, promoting angiogenesis and fibrosis progression [102–104]. The synchronistic expression of CD147 in both HCs and LSECs suggests its regulatory role in HCs–LSECs interactions, which may represent a new mode of HCs–LSECs crosstalk.

LSECs regulate hepatocyte proliferation and immune interactions through activin A and integrin β1 (ITGβ1)-mediated signaling. Yosif et al. demonstrated that KLF2 upregulates activin A expression and secretion in LSECs, exerting an anti-proliferative effect on hepatocytes. While KLF2 expression does not significantly influence capillary density or fibrosis, it induces an inhibitory secretome that suppresses liver regeneration [105]. In hepatic lipotoxicity, ITGβ1 plays a key role in immune cell recruitment. Lipotoxic stress in hepatocytes activates ITGβ1, promoting its endocytic trafficking and release via EVs. These EVs enhance monocyte adhesion to LSECs through ITGα9β1–VCAM1 interactions, contributing to hepatic inflammation and endothelial dysfunction [106] (Fig. 4).

### 3.3. Intercellular communication between LSECs and immune cells

LSECs actively interact with immune cells, including KCs, T cells and neutrophils, playing a crucial role in inflammation, fibrosis, and regeneration. These interactions are mediated through cytokines, adhesion molecules, EVs and mechanotransduction pathways (Fig. 5).

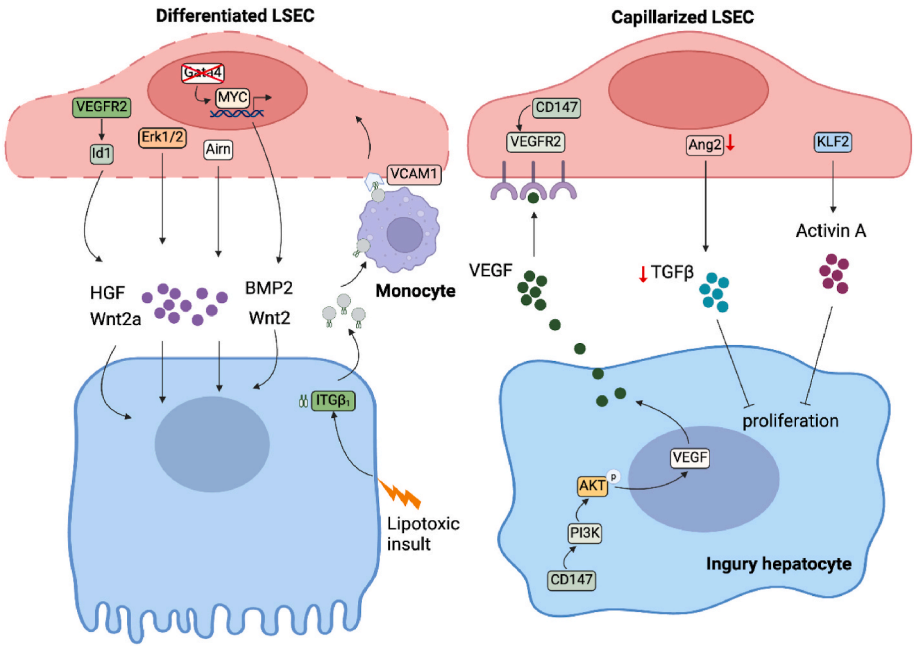


**Fig. 4.** Communication between LSECs and HCs. LSECs-HCs interactions regulate the balance between liver regeneration and fibrosis. Differentiated LSECs promote HCs proliferation by secreting Wnt2, HGF, and BMP2. Lipotoxic HCs-derived EVs, carrying ITGβ1, enhance monocyte adhesion to LSECs, contributing to inflammation. CD147-stimulated HCs promote LSECs capillarization via the PI3K/AKT/VEGF-A/VEGFR2 pathway, exacerbating fibrosis. Reduced TGF-β signaling impairs liver regeneration and accelerates fibrosis, while KLF2 induces an antiproliferative secretome, and activin A further suppresses HCs proliferation, shifting the balance toward fibrosis progression.

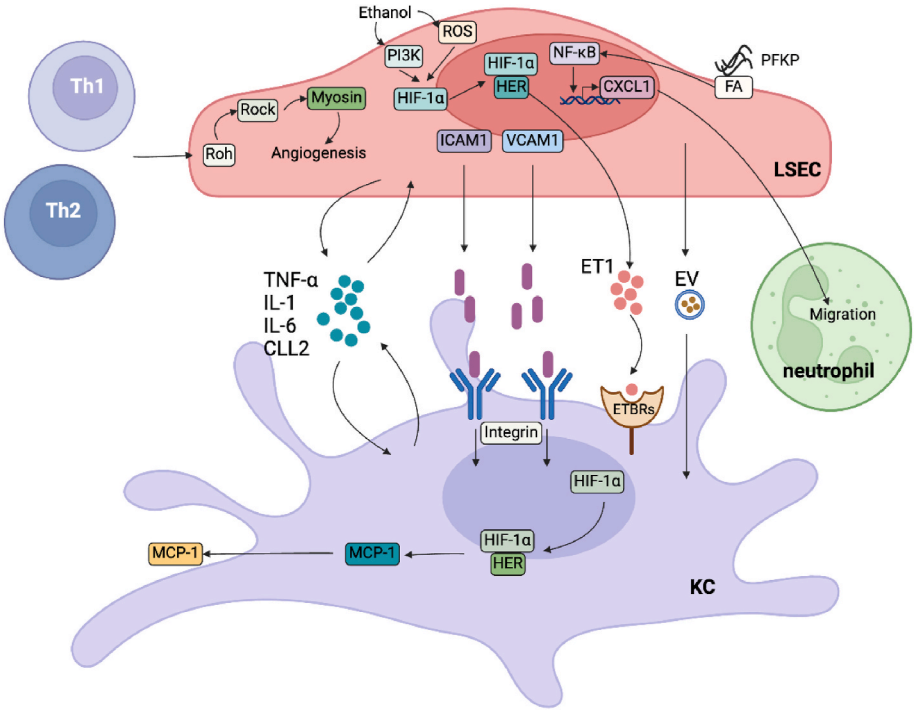


**Fig. 5.** Intercellular communication between LSECs and immune cells. LSECs engage in complex interactions with KCs, T cells, and neutrophils, shaping liver function and disease progression. ICAM-1 and VCAM-1 on KCs bind integrins, facilitating direct KCs-LSECs adhesion. LSECs-derived ET-1 interacts with ETR1 on KCs, contributing to sustained liver injury. While LSECs-derived EVs suppress KCs proinflammatory gene expression, LSECs can also secrete inflammatory mediators that activate KCs. Th1 and Th2 cells modulate LSECs angiogenesis via the Rho-ROCK-myosin pathway. Additionally, glycolytic enzyme PFKP recruitment to focal adhesions activates NF-κB signaling, upregulating CXCL1 and promoting neutrophil migration, further exacerbating inflammation and fibrosis.

KCs, the resident hepatic macrophages, are key regulators of immune surveillance and fibrosis progression. Under pathological conditions such as viral hepatitis and alcohol-induced injury, KCs secrete proinflammatory cytokines, including TNF-α and IL-1, which activate HSCs and promote fibrosis [107,108]. KCs are considered a key factor in the initiation and progression of fibrosis [109]. They are attached to the

sinusoidal endothelial layer and induce the proliferation and migration of LSECs by expressing various angiogenic factors, thus accelerating tissue recovery after acute injury [110]. Additionally, T cells and neutrophils play a crucial role in initiating and aggravating hepatic fibrosis by modulating immune responses, inflammation, and cytokine release.

LSECs modulate KCs recruitment through MMPs and TIMPs. VEGF enhances sinusoidal permeability and facilitates monocyte/macrophage recruitment via the CXCL9–MMP13 axis [111]. Recruitment of the monocyte–macrophage lineage by controlling the secretion of different MMPs and TIMPs plays a crucial role in liver regeneration [112]. A pro-regenerative LSECs phenotype is characterized by increased MMP-2, MMP-4, and MMP-13 expression and downregulated TIMP-1 and TIMP-2, promoting hepatic vascularization and reducing fibrosis [113,114].

Activated KCs generate ROS and proinflammatory cytokines that amplify hepatic injury. LSECs respond by secreting TNF-α, IL-6, IL-1, and CCL2, further stimulating KCs activation [115–117]. TNF-α upregulates intracellular adhesion molecule-1 (ICAM-1) on LSECs, enhancing neutrophil adhesion, extravasation, and hepatic inflammation [118,119]. Additionally, ethanol-induced HIF-1α activation in KCs upregulates ET-BR, enhancing ET-1/MCP-1 signaling and promoting neutrophil infiltration into sinusoids, exacerbating liver injury [120]. LSECs-derived EVs have been shown to downregulate proinflammatory gene expression in KCs, suggesting a potential anti-inflammatory role, though further investigation is needed to elucidate their precise function in liver pathology [89].

T cells and neutrophils play opposing roles in hepatic fibrosis through interactions with LSECs. Th1 cells promote LSECs capillarization via the Rho–ROCK–myosin pathway, enhancing angiogenesis and fibrosis, whereas Th2 cells exert antifibrotic effects by preserving fenestrae [121]. Additionally, Notch ligand DLL4, LSECs-derived TGF-β, and endogenous LXR ligands are essential for KCs maintenance and function [122].

Matrix stiffness influences LSECs-immune cell interactions through mechanotransduction pathways. The glycolytic enzyme phosphofructokinase 1 isoform P (PFKP) is recruited to focal adhesions (FAs) in response to increased stiffness, promoting actin polymerization and NF-κB activation. This induces CXCL1 expression, driving neutrophil recruitment, portal hypertension, and early fibrosis progression [71]. Furthermore, upregulated ICAM-1 and VCAM-1 expression in KCs suggests direct KCs-LSECs adhesion as a contributor to hepatic fibrosis [123].

LSECs play a central role in hepatic immune regulation by modulating interactions with KCs, T cells, and neutrophils. These interactions influence fibrosis progression, inflammation, and tissue repair. However, the precise mechanisms of LSECs-mediated immune regulation in chronic liver disease remain incompletely understood, necessitating further investigation into their therapeutic potential.

## 4. Therapeutic strategies targeting LSECs dysfunction

Recent advances in understanding the pathophysiological roles of LSECs have highlighted their potential as central therapeutic targets in hepatic fibrosis. LSECs dysfunction—manifested as capillarization, angiogenesis, autophagy, EndMT and senescence—drives fibrotic progression and alters hepatic microvascular homeostasis. A growing array of molecular, pharmacological, and genetic strategies are being explored to restore LSECs function. Below, we summarize these therapeutic approaches and their translational challenges.

### 4.1. Senolytic therapies

Senescence-associated LSECs accumulate in chronic liver injury and promote fibrogenesis through persistent secretion of SASP cytokines and impaired regenerative signaling. Senolytic agents such as Navitoclax/ABT-263and dasatinib plus quercetin (DQ) have been shown to selectively eliminate $p16^{High}$ LSECs, reduce collagen I/III deposition, and restore fenestration [124,125]. DQ additionally reverses epigenetic senescence via the Notch–Hes1–EZH2 axis [125]. Importantly, a recent breakthrough study by Amor et al. demonstrated that engineered CAR T cells targeting uPAR, a surface marker upregulated in various senescent cell types, can effectively eliminate senescent cells in fibrotic livers. Although the study did not specifically examine senescent LSECs, the uPAR-based strategy provides a conceptual framework for immunotherapeutic clearance of senescent endothelial populations in hepatic fibrosis [126]. Nevertheless, risks such as off-target toxicity, DAMP-mediated inflammation, and heterogeneous zonal responses remain significant clinical barriers.

### 4.2. Modulation of oxidative and inflammatory pathways

Oxidative stress is a pivotal driver of LSECs capillarization. Targeting TXNIP, a key redox regulator, has been shown to restore eNOS activity, suppress TAK1/JNK-mediated inflammation, and reduce fibrotic signaling in LSECs [59]. Tofogliflozin, an SGLT2 inhibitor, improves endothelial function by enhancing antioxidant defenses and reducing LSECs-mediated HSCs activation, particularly in models of portal hypertension [127]. However, effective and LSECs-specific delivery systems remain an unmet need.

### 4.3. Targeting pathological angiogenesis

Pathological angiogenesis contributes to LSECs remodeling and fibrosis. Nanoparticle-mediated delivery of miR-30c to LSECs inhibits the DLL4/Notch pathway, suppressing neovascularization and ameliorating hepatic fibrosis [128]. Altogether, LSECs are directly involved in hepatic angiogenesis. Additionally, curcumol inhibits KLF5-dependent angiogenesis by blocking ROS/ERK signaling [129,130] and disrupting the KLF5/LDH-A feedback loop, thereby suppressing glycolysis-driven angiogenesis and fibrosis progression [131]. Despite encouraging preclinical outcomes, curcumol faces challenges related to bioavailability and formulation stability.

### 4.4. Metabolic and autophagic reprogramming

Fibrotic LSECs demonstrate increased glycolytic flux and dysfunctional autophagy. Inhibiting PFKP normalizes LSECs metabolism, reduces pro-inflammatory cytokine release, and improves vascular compliance [71]. Similarly, Duan et al. demonstrated that senescent LSECs accumulate in the late phase of liver regeneration post-PHx, with Notch signaling mitigating senescence through the Sirt1–P53–P21 or Sirt1–P16 axis, thereby promoting regeneration [132,133]. Interestingly, autophagy inhibition can also be beneficial in specific contexts—such as by preventing Cav-1 degradation, thereby stabilizing F-actin and preserving nitric oxide-dependent signaling to maintain LSECs fenestration—highlighting the context- and stage-dependent nature of autophagy's role in fibrosis progression [134].

### 4.5. Extracellular vesicle (EV)-Based interventions

LSECs-derived EVs mediate intercellular signaling with HSCs and immune cells. EVs from healthy LSECs are enriched in miR-30c and tropomyosin-1, which suppress TGF-β/Smad3 and Notch signaling, thereby reducing HSCs activation and fibrogenesis [128,135]. Recent studies show that LSECs-derived EVs can modulate hepatic immunity by reprogramming KCs. Shimizu et al. found that LSECs-EVs enriched in miR-223 suppress NF-κB signaling, reduce TNF-α and IL-6 levels, and promote an anti-inflammatory KCs phenotype in sepsis models. Systemic administration of these EVs alleviated liver inflammation and improved survival, suggesting a novel immune-regulatory role for LSECs-EVs in liver injury [136]. Moreover, EVs serve as promising delivery platforms for CRISPR/Cas9 ribonucleoproteins (RNPs), enabling

efficient, non-viral in vivo editing of fibrogenic genes such as PDGFRB, with minimal off-target effects [137]. However, delivery efficiency is challenged by ECM stiffening and zonation-dependent EV uptake.

Taken together, LSECs-directed therapies encompass a broad spectrum of promising modalities—from small molecules and gene editing to engineered biologics and nanomedicine. Their successful translation will depend on the integration of stage-specific, zone-specific, and cell-selective strategies, alongside the advancement of delivery systems and precision diagnostics.

## 5. Conclusion

LSECs are central regulators of hepatic homeostasis, orchestrating complex interactions with HCs, HSCs, and immune cells. Their phenotypic alterations—including capillarization, angiogenesis, EndMT, autophagy dysregulation, and senescence—play crucial roles in the initiation and progression of liver fibrosis. Accumulating evidence highlights the dynamic and bidirectional communication between LSECs and other hepatic cell types through soluble factors, adhesion molecules, and extracellular vesicles. Understanding these interactions provides a foundation for identifying novel therapeutic targets.

While significant progress has been made, several important questions remain unresolved. For example, what determines whether LSECs dysfunction promotes fibrosis or regeneration under chronic liver injury? Can LSECs senescence be reversed pharmacologically to enhance endothelial plasticity and repair capacity? Are there stage-specific therapeutic windows during which targeting capillarization, angiogenesis, or inflammatory activation of LSECs would be most effective? Recent single-cell and spatial transcriptomic studies have begun to resolve the zonation-dependent transcriptional heterogeneity of LSECs subpopulations [2,138], identifying distinct phenotypes across periportal, midlobular, and pericentral zones [139]. These studies revealed novel LSECs markers such as Oit3 [3], and provided evidence that specific subtypes exhibit divergent pro- or anti-fibrotic signaling profiles depending on microenvironmental cues and disease stages. This deeper understanding opens new avenues for spatially-targeted antifibrotic strategies. Future studies integrating single-cell profiling, lineage tracing, and spatiotemporal modeling will be essential to unravel the context-dependent roles of LSECs in hepatic fibrosis and regeneration. A deeper understanding of these mechanisms will open new avenues for vascular-targeted antifibrotic therapies and liver repair strategies.

## CRediT authorship contribution statement

**Ting Chen:** Writing – review & editing, Writing – original draft, Funding acquisition. **Huan Zhang:** Data curation. **Wenqi Shan:** Data curation. **Jinxue Zhou:** Supervision. **Yanwen You:** Project administration.

## Availability of data and materials

Not applicable.

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## Declaration of competing interest

The authors declare no conflict of interest.

## Abbreviations

A-FABP Adipocyte fatty acid-binding protein
Airn Antisense Igf2r RNA
AKAP12 A-kinase anchoring protein 12
Ang-1 Angiopoietin-1
BMP9 Bone morphogenetic protein 9
BRG1 Brahma related gene 1
Cav-1 Caveolin-1 cGMP: Cyclic guanosine monophosphate
COUP-TFII Chicken ovalbumin upstream promoter-transcription factor II
CXCR C-X-C chemokine receptor type
DDR2 Discoidin domain receptor 2
DQ dasatinib plus quercetin
ECM Excessive extracellular matrix
Egr1 Early growth response factor 1
EndMT Endothelium-to-mesenchymal transition
ERK Extracellular signal-regulated kinase
EVs Extracellular vesicles
FN1 Fibronectin1
FμNs Fibrotic microniches
GATA4 GATA Binding Protein 4
HB-EGF Heparin-binding EGF-like growth factor
HMGB1 High-mobility group box 1
HSCs Hepatic stellate cells
ICAM-1 Intracellular adhesion molecule-1
ITG$\beta_1$ Integrin b1
IVA-PLA2 IVA phospholipase A2
JAM-A Junctional adhesion molecule A
JNK c-Jun N-terminal kinase
KCs Kupffer cells
KLF2 Kruppel-like factor 2
LECT2 Leukocyte cell-derived chemotaxin 2
LPS Lipopolysaccharide
LSECsS Liver sinusoidal endothelial cel1s
MAPK Mitogen-activated protein kinase
MKL1 Megakaryocytic leukemia 1
MMP Matrix Metallo proteinase
NF-kappaB Nuclear factor kappa B
NO Nitric oxide
PDGF Platelet derived growth factor
PLVAP Plasmalemma-vesicle-associated protein
P13K/AKT Phosphatidylinositide 3-kinases/protein kinase B
PPARγ Peroxisome-proliferator activated receptor gamma
PROX1 Prospero-related homeobox 1
PTCH1 Patched1
PVT1 Plasmacytoma variant translocation gene 1
PFKP phosphofructokinase 1 isoform P
Rab7 Member RAS oncogene family
Rac1 Ras-related C3 botulinum toxin substrate 1
ROS Reactive oxygen species
S1pr2 Sphingosine-1-phosphate receptor 2
SASP Senescence-associated secretory phenotype
Sirt1 Silent information regulator sirtuin 1
sGC Soluble guanylate cyclase
SK1 Sphingosine kinase 1
STAT3 Signal transducer and activator of transcription 3
TAK1 Transforming growth factor beta-activated kinase 1
TGF-β Transforming growth factor-β
TLR-4 Toll-like receptor 4
TNF Tumor necrosis factor
TXNIP Thioredoxin-interacting protein
VEGF Vascular endothelial growth factor
VCAM1 Vascular cell adhesion molecule 1
Zeb Zinc finger E-box-binding homeobox

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